ASSOCIATION OF β_2-ADRENERGIC RECEPTOR HAPLOTYPES WITH DRUG RESPONSE

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Field of the Invention

This invention relates to the fields of genomics and pharmacogenetics. More specifically, the present invention relates to polymorphisms and haplotypes of the β_2-adrenergic receptor gene and their use as predictors of disease susceptibility and response to β-agonists.

Background of the Invention

The β_2-adrenergic receptor (β_2AR) is a G protein coupled receptor that mediates the actions of catecholamines in multiple tissues and thus plays important roles in regulating cardiac, vascular, pulmonary, and metabolic functions. An abnormal level of expression of β_2AR is believed to be a risk factor for or to modify the severity of a number of diseases and conditions, including congestive heart failure, arrhythmia, ischemic heart disease, hypertension, migraine, asthma, chronic obstructive pulmonary disease (COPD), anaphylaxis, obesity, diabetes, myasthenia gravis, and premature labor.

The β_2AR is encoded by an intronless gene on chromosome 5q31-32 (Kobilka, B.K. et al., *Proc.Natl.Acad.Sci., USA* 84:46-50, 1987). Several single nucleotide polymorphisms (SNPs) in the coding block of the β_2AR gene that lead to significant genetic variability in the structure of the β_2AR protein in the human population have been reported (Reihsaus, E. et al., *Am J Resp Cell Mol Biol* 8:334-339, 1993; Liggett, S.B., *News in Physiologic Sciences* 10:265-273, 1995; and GenBank accession numbers AF022953.1 GI:2570526; AF022954.1 GI:2570528; and AF022956.1 GI:2570532). These SNPs are located at nucleotides 46 (A or G), 79 (C or G), and 491 (C or T) of the β_2AR coding sequence, and result in variation that occurs in the amino-terminus of the receptor at amino acids 16 (Arg or Gly) and 27 (Gln or Glu) and in the fourth transmembrane spanning domain at amino acid 164 (Thr or Ile), respectively. These amino acid variants have clear phenotypic differences as demonstrated by recombinant cell studies (Green, S.A. et al., *Biochem* 33:9414-9419, 1994; Green, S.A., et al., *J Biol Chem* 268:23116-23121, 1993), primary cultures of cells endogenously expressing these variants (Green, S.A., et al., *Am J. Resp Cell Mol Biol* 13 :25-33, 1995), and transgenic mice overexpressing the Thr164 or Ile164 receptors in the heart (Turki et al., *Proc. Natl. Acad. Sci., USA* 93:10483-10488, 1996). In addition, a synonymous polymorphism of C or A at nucleotide 523 in the coding sequence has been reported to be associated with altered responsiveness to salbutamol in Japanese families (Ohe, M. et al., *Thorax* 50:353-359, 1995).